PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/003888	13.04.2005	14.04.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/54, C12N15/11

Applicant
F. HOFFMANN-LA ROCHE AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Strobel, A Telephone No. +49 89 2399-7362

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/003888

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/003888

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18, 19,20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	19,20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Re Item IV.

The separate inventions/groups of inventions are:

Claims 1-18:

Expression system comprising one or several nucleic acids that comprise

a) at least one nucleic acid for a IL-15/Fc fusion protein
b) at least one promoter
and
c) at least one nucleic acid for a CD5 leader

Technical problem to be solved in view of the prior art: see point 3. under item V.

Claims 19, 20:

Use of a CD5 leader for the expression of a protein in CHO cells and their derivatives, in particular CHO-K1 cells.

Technical problem to be solved in view of the prior art: expression of any protein using the CD5 leader sequence. This problem is trivial in view of D2 which describes a CD5-Fc fusion protein.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

For the requirement of unity to be fulfilled according to Article 17 and Rule 13.1 PCT, the different groups of inventions present in the claims have to be linked by a special common or corresponding technical feature. A special common technical feature is a technical feature that makes a contribution to the teaching of the prior art, i.e. it has to be novel and inventive. In the present case the common technical feature of the independent claims 1 and 19 consists of the use of a CD5 leader for expression of proteins. Said common technical feature is, however, not novel in view of D2 (Sutherland et al., see abstract and materials and methods section page 1807), in which publication the cDNA of said leader is fused to that of an IgG2 protein and expressed in murine cells.

Re Item V.

1 **Reference is made to the following documents:**

D1 : YON SU KIM ET AL: "Targeting the IL-15 receptor with an antagonist IL-15 mutant/Fcgamma2a protein blocks delayed-type hypersensitivity" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 160, no. 12, 15 June 1998, pages 5742-5748

D2 : SUTHERLAND ROBYN M ET AL: "Protective effect of CTLA4Ig secreted by transgenic fetal pancreas allografts" TRANSPLANTATION (BALTIMORE), vol. 69, no. 9, 2000-05-15, pages 1806-1812

D3 : KIM Y S ET AL: "IMMUNOGLOBULIN-CYTOKINE FUSION MOLECULES: THE NEW GENERATION OF IMMUNOMODULATING AGENTS" TRANSPLANTATION PROCEEDINGS, ORLANDO, FL, US, vol. 30, no. 8, 1998, pages 4031-4036

D4: US5977318

D5: US5977307

2. **Novelty**

Claim 1 is novel (fulfilment of Article 33(2) PCT) because no prior art document discloses the combination of an IL15 - Fc fusion protein with a CD5 leader sequence attached to it. As a consequence, dependent claims 2-10 and 12-14 novel

This also renders independent claim 11 as well as independent method claim 15 with dependent claims 16 and 17 and independent claim 18 novel.

3. **Inventive step**

D1 as well as D3 describe IL15-Fc fusion proteins. These fusion proteins are said to be characterised by a prolonged half life in the bloodstream, which is regarded as an advantageous feature in various therapeutic applications (D1, abstract lines 6-7, figure 5; D3, page 4033, right-hand column, last paragraph to page 4035, right-hand column, second paragraph with tables 2-4).

D1 moreover describes an expression construct of a mutant human IL15 cDNA fused to a murine Fcgamma2 cDNA cloned into a eukaryotic expression plasmid carrying a CMV promoter, an Igkappa leader sequence (fused to the fusion protein construct) and a selection marker (D1, page 5743, left-hand column, second paragraph).

This means that the only difference between D1 and D3 on the one hand and claim 1 on the other hand is the presence, in claim 1, of a different signal peptide

as a leader sequence, namely the leader sequence of the CD5 protein.
The technical effect of said difference is an increased secretion of the IL15-Fc fusion protein when expressed in eukaryotic cells, as can be derived from page 22, line 16 to page 23, line 13 of the description.
Given that neither D1 nor D2 mention the problem of increasing expression efficiency of the described fusion proteins and that D3, on the other hand, which describes a CD5-Fc fusion peptide which is secreted from producing cells, is directed to a different technical field, namely the role of a B7 receptor subtype, CTLA4, in pancreatic allograft rejection, thus not making a combination of either D1 or D3 with D2 obvious, the subject-matter of claim 1 is considered to be inventive (fulfilment of Article 33(2) PCT).
As a consequence, claims 2-18 are also inventive.

D4 and D5 describe fusion proteins expressed in CHO cells which are cloned into an expression vector comprising the coding sequence for a CD5 leader peptide that controls the secretion of the fusion proteins (D4, column 7 lines 18-35, column 10, lines 44-55; D5, column 20, line 64 - column 21, line 22 in connection with figure 8).
In view of D4 and D5, the additional features of the present claims 19 and 20 are either trivial or conventional in the art or within the competence of a skilled man seeking to improve the prior art processes mentioned in the search report and in the present opinion, so that the subject-matter of said claims also lacks an inventive step (Article 33(3) PCT)

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
EP20030750224	2005-07-05	2003-10-13	2002-10-14